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Pharmacogenetic Analysis of CYP2D6 Variability in Kurdish Women Receiving Tramadol after Cesarean Delivery

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ABSTRACT

CYP2D6, a liver enzyme, plays a key role in metabolizing a range of drugs, including antidepressants, β-blockers, tamoxifen, and opioids such as tramadol and codeine, with notable inter-individual differences in drug response due to its high genetic polymorphism. This study investigated CYP2D6 polymorphisms in Kurdish women receiving tramadol after cesarean delivery. Forty participants from Maternity Teaching Hospital provided DNA samples, which were genotyped for CYP2D6 using polymerase chain reaction. Based on their CYP2D6 activity scores, participants were categorized into distinct phenotype groups. Analgesic efficacy and adverse effects were evaluated at 1 and 6 hours after tramadol administration. The CYP2D641 allele was the most prevalent (26.25%), with thirteen genotypes identified, and no ultrarapid metabolizers were detected among the participants. Poor metabolizers reported the highest mean visual analog scale scores at 1 hour (5.33 ± 1.70) and at 6 hours (5.53 ± 1.05). However, the occurrence of side effects did not significantly differ between phenotype groups. The findings indicate that CYP2D6*41 is the most common allele in this population, with poor metabolizers experiencing greater pain, highlighting that CYP2D6 polymorphism influences tramadol analgesic efficacy without affecting the incidence of side effects.

Keywords: CYP2D6, Tramadol analgesia, Pharmacogenomics, SNP, Side effects

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Introduction

Pain is described by the International Association for the Study of Pain (IASP) as an unpleasant sensory and emotional experience, and both IASP and the World Health Organization (WHO) emphasize that effective management of postoperative pain constitutes a fundamental human right, critical for recovery and reducing healthcare costs, especially in low-resource settings [1]. Despite available interventions, patients frequently experience pain during hospital stays, often due to reluctance to seek care—either underestimating their discomfort or avoiding the financial burden of treatment [2]. In other cases, healthcare providers may inadequately address pain due to limited clinical experience or lack of appropriate treatment protocols [3].

Women undergoing cesarean sections (CS) generally report more intense postpartum pain than those delivering vaginally without complications. Current evidence supports the use of stepwise, multimodal analgesic regimens that minimize opioid exposure as the most effective strategy for post-cesarean pain control [4]. Among analgesics, tramadol is frequently preferred because it is centrally acting, effective against moderate to severe pain, and has a better tolerability and lower toxicity profile compared to conventional NSAIDs [5]. In the liver, tramadol is metabolized by the cytochrome P450 2D6 (CYP2D6) enzyme via O-demethylation to form O-desmethyltramadol (M1), the major active metabolite, which exhibits 200–400 times greater affinity for the μ-opioid receptor than tramadol itself [6, 7].

Genetic variability in CYP2D6 is a major factor influencing tramadol efficacy. Patients with poor metabolizer (PM) or ultrarapid metabolizer (UM) phenotypes often require more complex management, incur higher treatment

costs, and are at greater risk of adverse effects compared to intermediate (IM) or normal metabolizers (NM) [8-10].

Currently, there is no published data evaluating the influence of CYP2D6 polymorphisms on tramadol effectiveness in post-cesarean patients. This study aims to assess the impact of CYP2D6 genetic variation on tramadol analgesia using the visual analog scale (VAS), along with monitoring any related adverse events, in postpartum women after CS in Erbil city.

Materials and Methods

Study design and participants

This prospective study included 40 Kurdish women admitted to Maternity Teaching Hospital in Erbil, Kurdistan Region, Iraq, for preoperative preparation for elective CS. Participants' ages ranged from 21 to 42 years, with a mean ± standard deviation of 31.45 ± 5.61 years.

Inclusion criteria

Eligible participants were aged 18–50 years, scheduled for elective CS, receiving tramadol for postpartum pain, and of Kurdish ethnicity. All participants were to receive standard 24-hour postpartum care and were administered 100 mg/2 ml of intravenous tramadol (Trodon Hemofarm) upon recovery of pain sensation.

Exclusion criteria

Participants were excluded if they had severe renal, hepatic, or respiratory disease; a history of seizures or psychiatric illness; an inability to provide consent; prior complicated surgery or prolonged hospitalization; neonatal complications; an inability to report VAS scores; a history of substance abuse; chronic opioid or alcohol use; or a known hypersensitivity to tramadol.

Ethical approval

Written informed consent was obtained from all participants for genetic analysis, clinical follow-up, and publication. The study was approved by the Medical Ethics Committee of Hawler Medical University/College of Medicine and conducted in accordance with the Declaration of Helsinki. The trial is registered at ClinicalTrials.gov (Identifier: NCT06814652).

Data collection and follow-up

Peripheral venous blood (2 ml) was collected from each participant into EDTA tubes. Part of the sample was used for routine hematologic analysis, while the remainder was preserved for DNA extraction following the clinical study procedures.

A structured questionnaire was completed preoperatively to record demographics (age, weight, smoking status), comorbidities (e.g., hypertension, diabetes), obstetric history (previous births or abortions), and medication use within the prior three months.

Postoperatively, participants were assessed 1 hour after tramadol administration for self-reported VAS pain scores, oxygen saturation (SpO_2), blood pressure, pulse rate, and any adverse effects. Additional clinical information, including gestational age, neonatal weight, and dexamethasone use, was obtained from hospital records. A follow-up assessment at 6 hours post-administration recorded the same parameters and noted any new side effects.

At 24 hours after tramadol administration, patients were re-evaluated either in person or via phone if discharged, to assess dietary intake, bowel movements, and occurrence of nighttime pain.

DNA extraction

Genomic DNA was obtained from 2 ml of whole blood using the Invitrogen DNA extraction kit (Thermo Fisher Scientific, USA, 2024). The quantity and purity of the isolated DNA were evaluated with the OneDrop TOUCH Pro spectrophotometer ((s Technologies Co., UK) at Exogen Laboratory, Zheen International Hospital, Erbil, Kurdistan Region, Iraq. Throughout the study, all extracted DNA samples and PCR reagents were maintained under refrigerated conditions to preserve stability.

Genotyping and sequencing

CYP2D6 variants were analyzed using the PGX-CYP2D6 XL StripAssay (ViennaLab Diagnostics GmbH, 2024), which combines PCR amplification with hybridization for mutation detection. This assay interrogates 19 polymorphic sites, allowing identification of both normal and mutant alleles, with each allele defined by a unique sequence signature. The method involves amplification of the CYP2D6 target regions, followed by hybridization to allele-specific probes immobilized on the test strips, as depicted in **Figure 1**.

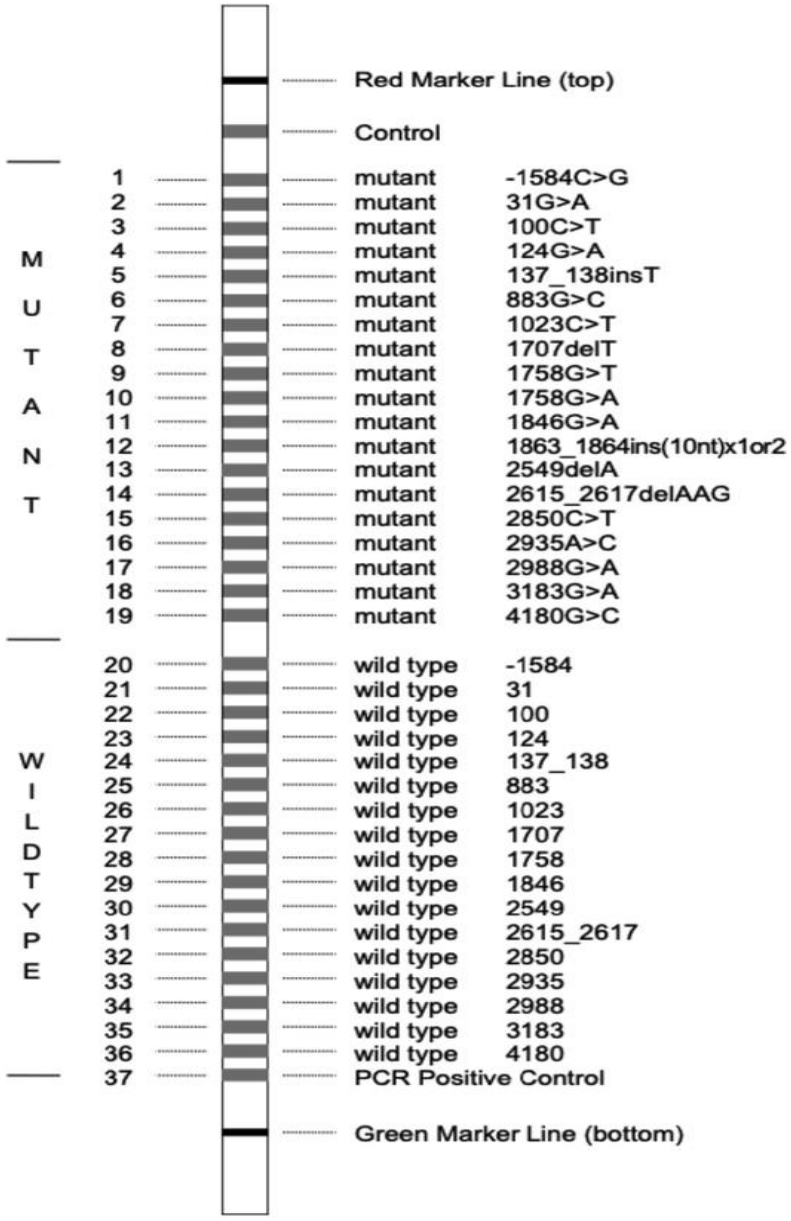


Figure 1. Design of the PGX-CYP2D6 XL StripAssay test strips (ViennaLab Diagnostics GmbH, 2024, Austria)

Allele assignment was determined based on the type of hybridization signals, covering *1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, *14, *15, *17, *29, *35, *39, *40, *41, *58, and *114. Once individual alleles were identified, they were combined to form diplotypes, such as *2/*4. In the final step, the dried strips were placed on a Collector sheet to read the genotype of each sample, with a purple-stained control line beneath the red marker confirming proper reagent functionality.

For confirmation and validation of ambiguous results—such as weak or overlapping signals—the extracted DNA samples were sent to the Intergen Genetics and Rare Diseases Diagnosis Center in Ankara, Turkey, for sequencing. Libraries were prepared using the Nextera DNA Flex Library Prep kit (Illumina, USA, 2025), and sequencing was

conducted on the MiSeq platform. The MiSeq system performed basecalling and demultiplexing to generate raw BCL files, which were subsequently converted to FASTQ format using Illumina software. Quality control checks were performed to assess read integrity, removing low-quality bases and adapter sequences, after which reads were aligned to a reference genome and converted into BAM format. Variant calling was then executed using GATK HaplotypeCaller, followed by quality filtering and variant annotation to interpret the results accurately. Participants were categorized into phenotypic groups according to their CYP2D6 genotypes and activity scores, following the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines [11]: poor metabolizers (PM, score = 0), intermediate metabolizers (IM, 0.25–1.25), normal metabolizers (NM, 1.25–2.25), and ultrarapid metabolizers (UM, >2.25).

Statistical analysis

Data analysis was conducted using SPSS version 27. For normally distributed paired data, a Student's t-test was employed, while the Kruskal–Wallis test was used for non-normal distributions, followed by Duncan's multiple range test to identify specific phenotypic group differences. Associations between genotypes and adverse effects were assessed with the chi-square test. Expected genotype frequencies were calculated using the Hardy–Weinberg equation ($p^2 + 2pq + q^2 = 1$), and chi-square testing evaluated adherence to equilibrium ($p > 0.05$), where:

- p = frequency of the dominant allele (A)
- q = frequency of the recessive allele (a)
- p + q = 1
- p^2 = homozygous dominant genotype (AA)
- 2pq = heterozygous genotype (Aa)
- q^2 = homozygous recessive genotype (aa)

Results and Discussion

Among the participants, 13 distinct CYP2D6 genotypes were detected: *1/*1, *2/*2, *2/*4, *4/*4, *4/*6, *4/*41, *7/*7, *9/*9, *10/*10, *15/*41, *17/*41, *39/*41, and *41/*41, as illustrated in **Figure 2**.

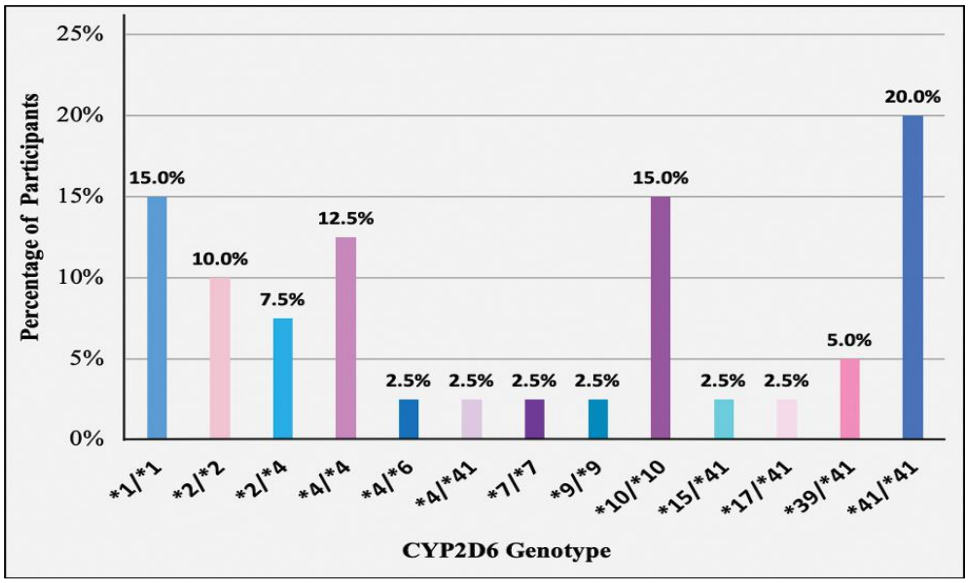


Figure 2. Distribution of CYP2D6 genotypes among post-cesarean participants.

The identified genotypes were categorized into three metabolic phenotype groups—poor metabolizers (PM), intermediate metabolizers (IM), and normal metabolizers (NM)—based on the CYP2D6 activity scoring system, as illustrated in **Figures 3 and 4.** No participants carried multiple copies of the wild-type allele, meaning that none had an activity score exceeding 2.25, and therefore, no individuals were classified as ultrarapid metabolizers (UM).

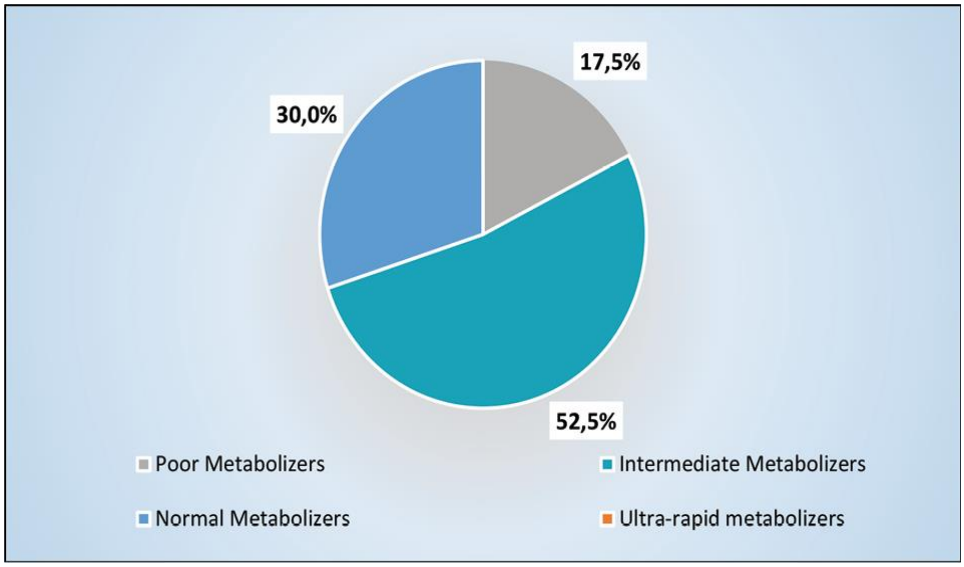


Figure 3. Frequency of CYP2D6 metabolic phenotypes among postpartum patients.

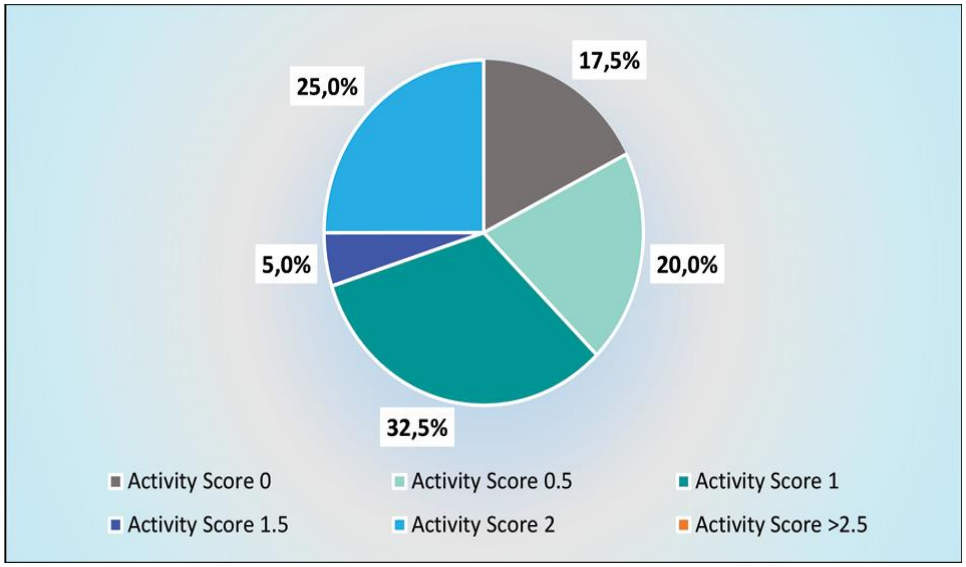


Figure 4. Distribution of CYP2D6 activity scores among study participants.

The predominant variant alleles identified were *41 (26.25%) and 4 (18.75%), as illustrated in **Figure 5.** CYP2D641 was the most frequent variant, with 20.00% of participants being homozygous intermediate metabolizers (*41/*41) and 5.00% being heterozygous normal metabolizers (*39/*41). The remaining carriers of the *41 allele were heterozygous intermediate metabolizers, paired either with a reduced-function allele (*17/*41) or a non-functional allele (*15/*41), each representing 2.50% of the cohort.

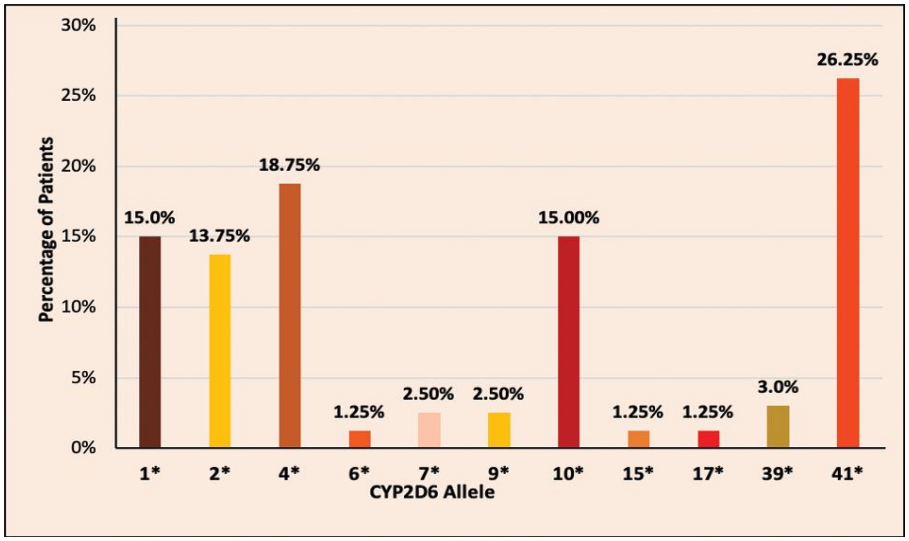


Figure 5. Distribution of CYP2D6 allelic genotypes among post-cesarean women.

The non-functional CYP2D6*4 allele was the second most prevalent variant in this cohort, with 12.50% of participants being homozygous poor metabolizers (*4/*4), 2.50% heterozygous poor metabolizers (*4/*6), and 7.50% heterozygous intermediate metabolizers (*2/*4), as depicted in **Figures 2 and 5**.

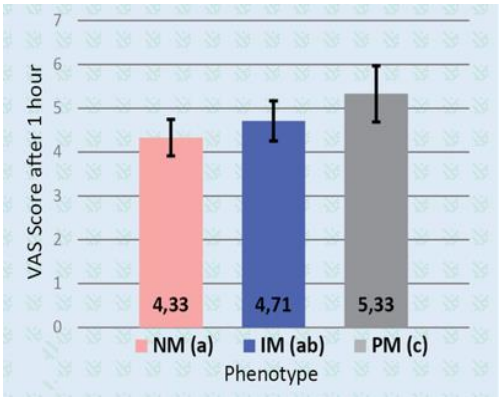
Analysis revealed no significant difference between the observed genotype frequencies and those expected under Hardy–Weinberg equilibrium (p = 0.18; **Table 1**), indicating that the study population conforms to Hardy–Weinberg equilibrium.

Table 1. Comparing genotype frequencies of this study and the expected frequencies by the Hardy–Weinberg equation.

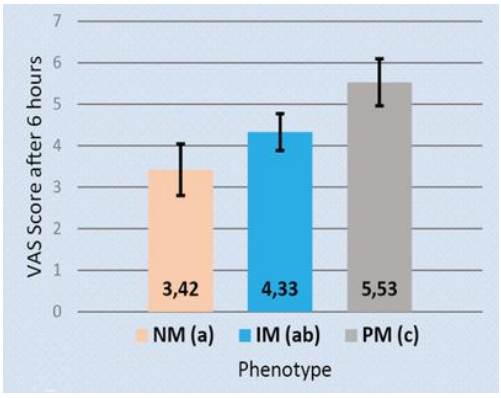
Genotype	Observed frequency	Expected frequency
AA	**12.0 (30.0%)**	**12.66 (31.64%)**
AB	**21.0 (52.50%)**	**19.69 (49.22%)**
BB	**7.0 (17.50%)**	**7.66 (19.14%)**

Data presented as frequency (percentage).

The visual analog scale (VAS) scores were measured for all three metabolic phenotype groups following administration of the same intravenous tramadol dose, yielding a mean score of 4.60 ± 1.89 at 1 hour post-administration **(Figure 6a)**. The highest pain score of 9 was reported by a poor metabolizer (PM), whereas the lowest score of 1 was recorded by an intermediate metabolizer (IM).



a)



b)

Figure 6. a) Mean VAS scores 1 hour after tramadol administration among different phenotypes; b) Mean VAS scores 6 hours after tramadol administration among different phenotypes. Data are expressed as mean ± standard error. IM: intermediate metabolizer; NM: normal metabolizer; PM: poor metabolizer; VAS: visual analog scale.

Pain intensity varied across participants. Among normal metabolizers (NMs), 75.0% reported moderate pain, while in the intermediate metabolizer (IM) group, 47.60% experienced moderate pain and 33.30% reported mild pain. The majority of poor metabolizers (PMs, 70.10%) indicated moderate pain.

At 6 hours post-tramadol, the mean VAS score for all participants was 4.20 ± 2.07 **(Figure 6b).** The highest recorded score was 8 in a PM patient, while the lowest score of 1 was reported by 7.50% of both PM and IM participants. Compared to the 1-hour assessment, 35.0% of participants experienced an increase in pain, whereas 60.0% reported reduced VAS scores. Mild pain was most commonly reported by 66.70% of NMs and 47.60% of IMs, while 57.10% of PMs continued to experience moderate pain.

Regarding adverse effects, drowsiness was the most frequently reported side effect at 1 hour, particularly among IMs (60.90%). Dry mouth was the second most common complaint, affecting 52.0% of IM participants, while sweating was the least observed side effect, primarily reported by NMs. Overall, PMs reported the fewest side effects **(Table 2).** Participants carrying the CYP2D6*41 allele exhibited the highest incidence of adverse reactions at both 1-hour and 6-hour intervals **(Table 3).**

Table 2. Comparing the number of participants (percentage) of side effects among different groups of phenotype.

Side effect		Normal metabolizer		Intermediate metabolizer		Poor metabolizer		p-value
		Yes	No	Yes	No	Yes	No	
After 1 hour	Drowsiness	5 (21.7%)	7 (41.2%)	14 (60.9%)	7 (41.2%)	4 (17.4%)	3 (17.6%)	0.42
	Dry mouth	3 (20.0%)	9 (36.0%)	8 (53.3%)	13 (52.0%)	4 (26.7%)	3 (12.0%)	0.60
	Sweating	3 (50.0%)	9 (26.5%)	2 (33.3%)	19 (55.9%)	1 (16.7%)	6 (17.6%)	0.53
After 6 hours	Dizziness	2 (15.4%)	10 (37.0%)	7 (53.8%)	14 (51.9%)	4 (30.8%)	3 (11.1%)	0.50
	Nausea	0.0%	12 (33.3%)	2 (50.0%)	19 (52.8%)	2 (50.0%)	5 (13.9%)	0.34

Table 3. Comparing the frequency (percentage) of adverse reactions among different allele carrier groups.

Side effect		CYP2D6*1	CYP2D6*2	CYP2D6*4	CYP2D6*10	CYP2D6*41
After 1 hour	Drowsiness	2 (8.7%)	5 (21.7%)	7 (30.4%)	4 (17.4%)	7 (30.4%)
	Dry mouth	2 (13.3%)	3 (20.0%)	6 (40.0%)	2 (13.3%)	4 (26.7%)
	Sweating	2 (33.3%)	0.0%	1 (16.7%)	0.0%	3 (50.0%)
After 6 hours	Dizziness	2 (15.4%)	0.0%	4 (30.8%)	2 (15.4%)	4 (30.8%)
	Nausea	0.0%	0.0%	1 (25.0%)	0.0%	2 (50.0%)

One hour following tramadol administration, the predominant adverse effects among participants were drowsiness (60.90%) and dry mouth (53.30%), particularly evident in the IM group. Sweating was reported the least, mostly in NMs, while PMs experienced the fewest overall side effects. Individuals carrying the CYP2D6*41 allele exhibited the highest incidence of adverse reactions at both evaluated time points.

After six hours, dizziness became the most frequently reported side effect, affecting 53.80% of the IM group, whereas nausea remained the least common reaction across all metabolizer categories.

This investigation assessed CYP2D6 single-nucleotide polymorphisms (SNPs) in 40 Kurdish post-cesarean patients from Erbil city, aiming to understand the variability in tramadol's analgesic effect and associated side effects. To the best of our knowledge, this is the first study examining the impact of CYP2D6 polymorphisms on post-cesarean pain management in the Kurdish population and, more broadly, in Iraq.

Based on the combination of alleles and enzyme activity, CYP2D6 phenotypes are classified as PM, IM, NM, and UM [12]. Within this cohort, the most frequent variants were the reduced-function CYP2D6*41 (26.25%) and the non-functional 4 allele (18.75%), while the CYP2D61 wild-type allele was the predominant functional form (15%).

These findings align with multiple population studies—Bosnian [13], Saudi Arabian [14], Turkish [15], Sri Lankan [16], and Han and Uighur groups—which reported CYP2D6 allele frequencies consistent with Hardy-

Weinberg equilibrium, suggesting genetic stability [17]. Deviations observed in Japanese populations may be explained by gene duplications or deletions [18]. Such genetic data are crucial for pharmacogenetic applications and individualized therapy.

Comparisons with other Middle Eastern populations revealed notable differences. The CYP2D6*1 allele appeared less frequently among Kurdish post-cesarean patients than in Persians (43.5–90.0%), Turks (32.0–87.8%), Saudi Arabians (78.4–79.1%), and Egyptians (47.7–85.1%) [19]. The *2 allele frequency was similar to the UAE (12.2%) but higher than in some regional populations, including Syrians (30.39%) [11, 19], Persians (32.0%), Turks (19.6–35.3%) [19], Algerians (28.3%), Egyptians (28.3%), and Palestinians (27.5%) [11]. The prevalence of the *4 allele in Kurds was comparable to Egyptians (9.6–22.0%) [11].

The *10 allele frequency was close to that observed in Iraqi Arabs (10.42%) [20], Turks (6.0–26.0%) [19], and Jordanians (14.8%) [11, 19], but lower than in Syrians [19], UAE, Saudi Arabians [11, 19], Algerians, Moroccans, Egyptians, and Palestinians [19]. This allele remains common in East Asia (China, Japan, South Korea) and has been heavily studied in pharmacogenetics over the past decade [17].

Lastly, the *39 allele was rare in this Kurdish cohort, comparable to the UAE (4.0%) [19], while it occurred more frequently in Iraqi Arabs (11.07%) [20].

The CYP2D6*41 allele frequency in the studied Kurdish population was similar to that reported in Iraqi Arabs (27.04%) [20] but appeared to be less frequent in other Middle Eastern populations, including Turkey [20], Saudi Arabia, UAE [11, 19], as well as Syria, Algeria, Egypt, Lebanon, and Palestine [11]. However, larger sample sizes may be needed to validate these findings in the Kurdish population.

These observations suggest that the genetic profile of Kurdish women undergoing cesarean sections aligns more closely with Iraqi Arabs, Persians, Turks, and other Arab populations, while also exhibiting notable differences indicative of ethnic and geographic genetic diversity. Overall, Kurds display closer genetic similarity to broader Middle Eastern populations, characterized by a lower prevalence of functional CYP2D6 alleles (*2 and *39) and a higher proportion of reduced-function alleles (*4, *10, and *41) [11, 19, 20].

The elevated occurrence of reduced-function alleles (*4, *10, and *41) among Kurdish post-cesarean women suggests a substantial fraction may exhibit altered drug metabolism, particularly affecting tramadol activation. This implies that Kurdish patients could be at an increased risk of reduced therapeutic efficacy or adverse effects when using CYP2D6-metabolized medications, highlighting the potential value of pharmacogenetic screening in this population. Additionally, the distinct Kurdish genetic profile underscores the importance of integrating these data into global pharmacogenomic databases.

Beyond tramadol, these allelic variants may also influence the metabolism of other CYP2D6 substrates, including tamoxifen and various antidepressants, emphasizing the potential utility of pharmacogenetic testing for optimizing drug safety and effectiveness in Kurdish women undergoing cesarean delivery.

The current study's VAS data revealed a significant difference in tramadol analgesic response between PM and NM genotype groups. Pain intensity scores were higher in PM patients, while IM patients experienced intermediate relief, and NM patients consistently reported the lowest pain scores at both 1-hour and 6-hour post-administration. Future studies incorporating UM patients with larger sample sizes would strengthen these findings and support individualized pain management strategies across broader clinical applications.

Specifically, the PM group demonstrated higher mean VAS scores at 1 hour (5.33 ± 1.70) and 6 hours (5.53 ± 1.05) following tramadol administration compared to other phenotype groups, whereas NM patients had lower mean scores at 1 hour (4.33 ± 1.44) and 6 hours (3.42 ± 2.15). Pain intensity followed a similar trend, being highest in PMs, lower in IMs, and lowest in NMs at both time points. These results indicate a clear phenotype correlation in post-cesarean analgesia, with pain relief improving as CYP2D6 metabolic activity increases, supporting the role of CYP2D6 genotype in guiding personalized opioid therapy.

Previous clinical studies corroborate these findings, demonstrating that CYP2D6 polymorphisms influence drug response. For instance, Wang *et al.* reported that UMs convert tramadol to its active metabolite O-desmethyltramadol more efficiently, leading to enhanced analgesic effects but also a higher risk of adverse events, while PMs produce lower plasma concentrations of M1, potentially diminishing analgesic response [21].

Notably, no significant differences in adverse effect incidence were observed among NM, IM, and PM groups in this study. To date, CYP2D6 polymorphism has not been investigated in the Iraqi post-cesarean population, and the current results align with prior findings regarding analgesic efficacy and tolerability reported by Lopes *et al.* (2020) [22].

Clinical guidelines suggest adjusting tramadol dosing or considering alternative analgesics for IM and PM patients, as these groups demonstrate higher plasma levels of the prodrug and slower clearance compared to NM and UM individuals [23]. Furthermore, IM and PM patients exhibited lower M1 metabolite concentrations at 30 minutes and 2 hours post-tramadol administration relative to NM and UM groups, with these differences diminishing after 2 hours [6].

One hour after tramadol administration, patients carrying the CYP2D6*10/10 genotype had a mean VAS score of 3.83 ± 1.84, compared with 4.53 ± 1.77 in those with the wild-type allele. At 6 hours post-administration, the CYP2D610/10 group recorded a mean VAS score of 4.0 ± 1.67, while the wild-type group had a score of 3.8 ± 2.34. The results indicated no statistically significant differences between the groups, suggesting that the CYP2D610/*10 genotype did not meaningfully influence tramadol analgesic response at either time point.

Previous studies on the impact of the CYP2D6*10/*10 genotype on tramadol analgesia in East Asian populations have yielded inconsistent findings. Xu *et al*. reported that individuals with the *10/*10 genotype experienced a higher frequency of adverse effects, such as nausea and vomiting [24], whereas Dong *et al.* [25]. observed that homozygous *10 carriers required higher tramadol doses to achieve adequate postoperative pain relief compared to wild-type individuals [25].

In the present study, no significant differences in adverse effect incidence were observed between CYP2D6*10/10 patients and other genotype groups, consistent with the findings of Wen *et al*. (2020) [24]. Notably, none of the CYP2D610/*10 participants reported nausea six hours after tramadol administration, whereas 10% of PM or IM patients experienced this effect. The routine pre-administration use of the antiemetic metoclopramide in all patients likely limited the detection of two common tramadol-related side effects—nausea and vomiting—within the first hour.

A major strength of this study is its focus on the influence of CYP2D6 genotype on tramadol analgesia, specifically in postpartum women, a population not extensively studied previously.

Conclusion

CYP2D6*41 was identified as the most prevalent allele among Kurdish post-cesarean women receiving tramadol, with PM patients exhibiting the highest pain scores. While CYP2D6 polymorphisms influenced analgesic effectiveness, they did not significantly affect the incidence of side effects.

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Conflict of Interest: None

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Ethics Statement: None

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